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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/594,427 | 07/17/2008 | Masashi Isozaki | 1029650-000178 | 2940 |

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| EXAMINER | |
|---|---|
| SCHULTZ, JAMES | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 11/05/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/594,427 | ISOZAKI ET AL. | |
| | Examiner | Art Unit | |
| | James (Doug) Schultz, PhD | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *7-9,13 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10-12 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed July 19, 2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed July 19, 2010 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application contains claims 7-9, 13, and 18 are drawn to an invention nonelected with traverse in the reply filed on December 22, 2009. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 10-12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haragai et al. (Pharmaceutical Research Volume 18, Number 9 / September, 2001, pages 1284-1290), in view of Mayer et al. (U. S. Patent Number 5,616,341). This rejection is repeated

for the same reasons of record as set forth in the action mailed April 19, 2010, and is reproduced below with responses to applicants traverse following.

The claims of the instant invention are drawn to a liposome preparation comprising a unilamellar vesicle formed from a lipid bilayer comprising a phospholipid as the main membrane component, and an interior aqueous phase in the vesicle at a pH of up to 5, wherein the liposome has a drug loaded therein, and wherein the vesicle is modified with a hydrophilic macromolecule only on its exterior surface, or the liposome preparation according to claim 1, wherein the drug is the one which is unstable at a pH higher than 5, or wherein the drug loaded is at a concentration of 0.05 mole / mole lipid, or wherein the drug loaded is at a concentration of 0.1 mole / mole lipid, or wherein the main membrane component is a phospholipid having a phase transition temperature of at least 50°C, or wherein the phospholipid is a hydrogenated phospholipid.

The invention also comprises the liposome preparation according to claim 1 wherein the lipid bilayer further comprises a basic compound containing a group selected from amino group, amidino group, and guanidino group as its component, or wherein the basic compound is 3,5-dipentadecyloxybenzamidine hydrochloride, or wherein the hydrophilic macromolecule is polyethylene glycol having a molecular weight of 500 to 10,000 Dalton, or wherein the , or wherein the liposome preparation has an average size of 40 to 140 nm, or 50 to 130 nm, or 60 to 120 nm. The invention also comprises the liposome preparation according to claim 1, wherein the interior aqueous phase has a pH of 2 to 5.

Haragai et al teach a liposome preparation comprising a unilamellar vesicle formed from a lipid bilayer comprising a phospholipid as the main membrane component, wherein the liposome has rhodamine loaded therein, and wherein the vesicle is modified with a hydrophilic

macromolecule only on its exterior surface which is PEG, wherein the compound comprises 3,5, 3,5-dipentadecyloxybenzamidine hydrochloride, and wherein the drug loaded is at a concentration of 0.02 mole / mole lipid, wherein the main membrane component is a phospholipid having a phase transition temperature of at least 50°C, and wherein the phospholipid is a hydrogenated phospholipid. Haragai also teaches liposome preparations having an average size of 100 nm.

Haragai does not teach the liposomes having an interior aqueous phase in the vesicle at a pH of up to 5, or wherein the drug is the one which is unstable at a pH higher than 5, or wherein the drug loaded is at a concentration of 0.1 or .5 mole / mole lipid.

Mayer et al. teaches liposomes comprising phosphatidylcholine having an interior aqueous phase at a pH of up to 5, which carries doxorubicin, which in order for the instant invention to be considered enabled, is unstable at a pH higher than 5.

Neither Mayer nor Haragai et al teach the drug loaded at a concentration of 0.1 mole / mole lipid.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate phosphatidylcholine into the liposomes of Haragai et al. since phosphatidylscholine is a well known phospholipid commonly used in the formulation of liposomes, as evidenced by its use in the liposomes of Mayer et al. The use of phosphatidylcholine is considered to be an art recognized equivalent and its use is considered to be one that would be reached in the process of routine optimization. Furthermore it would have been obvious to use such phosphatidyl containing low pH liposomes in the delivery of doxorubicin, since doxorubicin is a well-known anticancer treatment, the liposomal delivery of

which (at a low pH) is evidenced by Mayer et al. Haragai et al. also teach that their liposomes are effective delivery vehicles for many types of molecules. Finally, it would have been obvious to one of ordinary skill in the art to load the doxorubicin of Mayer et al at 0.1 or 0.5 mole/mole, since these amounts are within the range of amounts that would be reached upon the practice of routine optimization.

Response to Request for reconsideration

Applicants point out that Harigai et al. ("Harigai") teaches an interior aqueous phase using physiologic saline, which is not within the claimed pH limit of "up to 5", and that the liposomes of Harigai et al. are not loaded with a drug. Applicants argue that Harigai is thus not applicable to the instant claims, which require a liposome with an interior aqueous phase having a pH of up to five, and that further has a hydrophilic macromolecule attached to its exterior. Harigai is alleged to be limited to investigating the binding ability between liposomes and cells, is only tested in vitro, and has nothing to do with stability properties of liposomes, such as retentive the in blood, membrane stability, or storage stability.

In response, it is noted that the instant claims do not appear to recite anything relating to in vitro testing, retention in blood, or membrane or storage stability, and are thus directed to limitations not found in the claims. These arguments are not considered convincing therefore. It is agreed that Harigai is focused on the binding ability between liposomes and cells. However, it is not clear how Harigai can be considered irrelevant prior art because of this, since it is well known in the art that liposomes are widely used as drug delivery tools to assist with uptake of encapsulated material across the phospholipid bilayer and into the cellular environment. For example, the last line of the reference states "[t]hese results suggest that the preferential and

selective binding characters of PEG-coated TRX 20 liposomes will become useful tools for development of drug targeting system[s] in the future". Since Harigai thus envision their PEG-coated liposomes as useful in drug delivery, and since the instant claims embrace PEG-coated liposomes used in drug delivery, Harigai is considered to teach all elements of the claim except for a low internal aqueous phase pH.

This is taught by the secondary reference of Mayer et al. ("Mayer)". Mayer teach liposomes used in the delivery of a drug (e.g. doxorubicin among others), wherein the internal aqueous phase pH is below 5. Applicants argue that the reference of Mayer does not teach liposomes modified with PEG. This is not adopted. Applicants are referred to the 19th paragraph of the "Detailed Description of the Invention" where Mayer teaches that the liposomes may contain PEG modified cholesterol derivatives. While it may be inferred that applicants might argue that Mayer does not teach PEG confined to the outside surface only as claimed instantly, one of ordinary skill in the art would immediately understand that PEG is commonly used as a liposome targeting agent and would thus necessarily need to be put on the outside surface of such liposomes. Indeed, this is exactly what Harigai teaches.

Applicants argue that Mayer discusses only unmodified liposomes in blood stability and make no reference to modified liposomes. It is not clear what weight to give arguments directed to "blood stability", since as stated above, such a limitation does not appear in the instant claims. Furthermore, Mayer is not considered to be limited only to unmodified liposomes (as discussed above) since Mayer teaches that PEG-cholesterol may be used in the formulation of their liposomes, as claimed instantly. Accordingly, applicants conclusion that the references of Harigai and Mayer cannot be combined is not adopted. The argument that the rejection is based

on a mere conclusory allegation of obviousness is similarly not adopted, since to accept such a premise one would need to ignore the fact that A) Harigai teaches all elements of at least claim one, that is, a phospholipid containing liposome with an exterior PEG modification, with the exception of a low internal pH, and B) Mayer teaches all elements of at least claim one, that is a phospholipid containing liposome with a low internal pH, with the possible exception of a PEG moiety attached to the outside surface. Even here, the reference of Mayer is considered to teach the use of PEG-cholesterol in their liposomes, albeit without a clear reference that such a modification be should be confined exclusively to the outer surface. However, one of ordinary skill in the art would immediately understand that the teachings of both references are clearly and obviously interrelated, since both relate to the design of liposomes used in drug delivery. The rejection is maintained therefore.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 10-12, and 14-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,676,971, in view of Haragai et al. (Pharmaceutical Research Volume 18, Number 9 / September, 2001, pages 1284-1290), and Mayer et al. (U. S. Patent Number 5,616,341). This rejection is repeated for the same reasons of record as set forth in the action mailed April 19, 2010, and is reproduced below with responses to applicants traverse following.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are drawn to pegylated liposomes, which embrace the scope of the instant claims drawn to pegylated liposomes that have a pH up to 5, and contain doxorubicin. Although the patented claims to not teach liposomes that have a pH up to 5, and contain doxorubicin, this feature is disclosed above in the combinations of Haragai and Mayer et

al. as described above. Mayer et al. teaches liposomes comprising phosphatidylcholine having an interior aqueous phase at a pH of up to 5, which carries doxorubicin, which in order for the instant invention to be considered enabled, is unstable at a pH higher than 5. Haragai et al. teach the use of 3,5 pentadecyloxybenzamadine containing liposomes as taught above.

It would have been obvious to use 3,5 pentadecyloxybenzamadine-containing liposomes as taught by Haragai et al. with low pH interiors in the delivery of doxorubicin as taught by Mayer et al., since doxorubicin is a well-known anticancer treatment, the low pH liposomal delivery of which is also well known, as evidenced by Mayer et al.

Response to Request for reconsideration

Applicants have argued that the claimed invention is not obvious over the combination of Harigai and Mayer in view of US patent number 5,676,971. Applicants point to their arguments set forth in the obviousness rejection over Harigai and Mayer, wherein it is argued that the teachings of Harigai or Mayer separately or combined do not reach the instant invention. In response, applicants attention is directed to the response to those arguments, as they are believed to be addressed in full. These arguments have not been adopted as explained therein, and the present rejection is maintained accordingly.

## *Conclusion*

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James (Doug) Schultz, PhD whose telephone number is (571)272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James (Doug) Schultz, PhD/

Primary Examiner, Art Unit 1633